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Outcome predictors and patient progress following delivery in pregnant and postpartum patients with severe COVID-19 pneumonitis in intensive care units in Israel (OB-COVICU): a nationwide cohort study

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See Online for appendix

Summary

Background A key unresolved controversy in severe COVID-19 pneumonitis in pregnancy is the optimum timing of delivery and whether delivery improves or worsens maternal outcomes. We aimed to assess clinical data on every intensive care unit (ICU) day for pregnant and postpartum women admitted to the ICU with COVID-19, with a particular focus on the days preceding and following delivery.

Methods In this multicentre, nationwide, prospective and retrospective cohort study, we evaluated all pregnant women who were admitted to an ICU in Israel with severe COVID-19 pneumonitis from the 13th week of gestation to the 1st week postpartum. We excluded pregnant patients in which the ICU admission was unrelated to severe COVID-19 pneumonitis. We assessed maternal and neonatal outcomes and longitudinal clinical and laboratory ICU data. The primary overall outcome was maternal outcome (worst of the following: no invasive positive pressure ventilation [IPPV], use of IPPV, use of extracorporeal membrane oxygenation [ECMO], or death). The primary longitudinal outcome was Sequential Organ Failure Assessment (SOFA) score, and the secondary longitudinal outcome was the novel PORCH (positive end-expiratory pressure [PEEP], oxygenation, respiratory support, chest x-ray, haemodynamic support) score. Patients were classified into four groups: no-delivery (pregnant at admission and no delivery during the ICU stay), postpartum (ICU admission ≥1 day after delivery), delivery-critical (pregnant at admission and receiving or at high risk of requiring IPPV at the time of delivery), or delivery-non-critical (pregnant at admission and not critically ill at the time of delivery).

Findings From Feb 1, 2020, to Jan 31, 2022, 84 patients were analysed: 34 patients in the no-delivery group, four in postpartum, 32 in delivery-critical, and 14 in delivery-non-critical. The delivery-critical and postpartum groups had worse outcomes than the other groups: 26 (81%) of 32 patients in the delivery-critical group and four (100%) of four patients in the postpartum group required IPPV; 12 (38%) and three (75%) patients required ECMO, and one (3%) and two (50%) patients died, respectively. The delivery-non-critical and no-delivery groups had far better outcomes than other groups: six (18%) of 34 patients and two (14%) of 14 patients required IPPV, respectively; no patients required ECMO or died. Oxygen saturation (SpO_2), SpO_2 to fraction of inspired oxygen (FiO_2) ratio (S/F ratio), partial pressure of arterial oxygen to FiO_2 ratio (P/F ratio), ROX index (S/F ratio divided by respiratory rate), and SOFA and PORCH scores were all highly predictive for adverse maternal outcome ($p<0·0001$). The delivery-critical group deteriorated on the day of delivery, continued to deteriorate throughout the ICU stay, and took longer to recover (ICU duration, Mantel-Cox $p<0·0001$), whereas the delivery-non-critical group improved rapidly following delivery. The day of delivery was a significant covariate for PORCH ($p<0·0001$) but not SOFA ($p=0·09$) scores.

Interpretation In patients who underwent delivery during their ICU stay, maternal outcome deteriorated following delivery among those defined as critical compared with non-critical patients, who improved following delivery. Interventional delivery should be considered for maternal indications before patients deteriorate and require mechanical ventilation.

Funding None.

Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 virus is one of the defining public health emergencies of this century.[1] SARS-CoV-2 infection presented with a range of clinical manifestations, from asymptomatic or uncomplicated upper respiratory tract infection to severe pneumonitis, multiorgan failure, and death.[2,3] The epidemiology and disease severity of COVID-19 in pregnancy changed over time, with the emergence of different serotypes.[4] In the first two waves of the

Research in context

Evidence before this study

It is not known whether delivery improves or worsens maternal outcomes in severe COVID-19 pneumonitis. We searched PubMed on July 29, 2022, from database inception with no language restrictions, using the search terms (SARS-CoV-2 OR COVID-19) and (Pregnancy OR Postpartum) and ((Critical Care) OR (Intensive Care) OR (ICU)) and ((randomized controlled trial) OR (observational study) OR (retrospective study)). We found 248 relevant publications, of which there were no randomised controlled trials of critically ill pregnant patients, and no studies that evaluated any longitudinal outcomes following delivery.

Added value of this study

To our knowledge, this is the first comprehensive nationwide study of pregnant or postpartum patients admitted to the intensive care unit (ICU) due to severe COVID-19 pneumonitis, and the first study to assess longitudinal clinical and laboratory data for every day of ICU admission. Our longitudinal data suggest that critical patients (ie, those receiving invasive positive pressure ventilation [IPPV] or close to requiring IPPV) generally deteriorated on the day of delivery, took longer to recover, and had a worse maternal outcome, while all other patients improved rapidly following delivery.

Implications of all the available evidence

This study provides temporal evidence to suggest that interventional delivery should be considered for maternal indications before patients deteriorate to the point at which they require IPPV. Furthermore, in view of the high morbidity and mortality in our small postpartum group, and the higher severity they exhibited on admission to the ICU, we advocate a reassessment of ICU admission criteria for postpartum patients with COVID-19 pneumonitis and the provision of additional vigilance if they continue to be managed in a non-ICU setting.

pandemic, when wild-type SARS-CoV-2 and the D614G variants were prevalent, international studies reported varying degrees of severity of COVID-19 in pregnancy compared with the general population.[5–9] During subsequent waves, when alpha (B.1.1.7) and delta (B.1.617.2) variants were prevalent,[4,6,10–12] pregnant women had disproportionately high rates of intensive care unit (ICU) admission,[8,13–15] extracorporeal membrane oxygenation (ECMO) use,[11–13,15] and death.[12,13,16]

Multiple guidelines for managing COVID-19 in pregnancy were developed,[16–18] but their validity and generalisability has been limited by the rapid appearance of new viral variants and vaccines, changing the characteristics and outcomes of the disease.[16,19] In particular, there is no evidence to guide the timing of interventional delivery when pregnant women with severe COVID-19 pneumonitis should be considered for interventional delivery[12,20] and to indicate whether this leads to improved maternal outcomes.[12,21,22]

Improvement in maternal outcome could occur as delivery improves oxygenation (by increasing functional residual capacity) and ventilation (by improving lung mechanics).[23,24] Conversely, deterioration could occur due to transient autotransfusion that typically occurs in the first few days after delivery,[25,26] accompanied by increased venous filling pressures, ventricular stroke volume, and cardiac output. As severe COVID-19 pneumonitis is frequently characterised by impaired cardiovascular compliance,[27,28] autotransfusion could trigger cardiac failure and pulmonary oedema.[26] It is unknown which of these responses is predominant following delivery in pregnant women with severe COVID-19 pneumonitis.[12,29,30]

This study aimed to describe clinical details of critically ill pregnant or peripartum women with severe COVID-19 and to examine whether the effect of delivery on the clinical course (maternal improvement or deterioration) was affected by the severity of the disease at the time of delivery. The hypothesis was that the effect of delivery on maternal outcome depends upon illness severity at the time of delivery, and that pregnant patients with COVID-19 in the ICU, not yet needing mechanical ventilation, would improve following delivery (possibly due to improvement in functional residual capacity and respiratory mechanics). In patients already mechanically ventilated, or close to requiring ventilation, we hypothesised that the net effect would be more complex, with overall deterioration (possibly because intolerance to autotransfusion was predominant).

As a randomised controlled trial of interventional delivery in this patient population was not feasible,[31] we aimed to perform a national cohort study, including every ICU in Israel, to assess longitudinal data for every ICU day, with a particular focus on the days preceding and following delivery.

Methods

Study design

In this multicentre, nationwide, prospective and retrospective cohort study, we aimed to evaluate all ICU admissions of pregnant or peripartum women with COVID-19 pneumonitis in all ICU departments in Israel. Of 20 ICUs in Israel that accepted patients with COVID-19, five had no obstetric patients, one declined to participate, and one was inadvertently not approached. A total of 13 ICUs participated in the study. Institutional Review Board approval, with a waiver of patient consent, was obtained for each participating centre. Because approvals were obtained by participating centres at different times, patients were identified both prospectively and retrospectively; however, in both cases, data were collected after discharge from the ICU.

The study was designed using the STROBE checklist for reporting observational studies.[32]

Participants

We enrolled all consecutive patients meeting the inclusion criteria in participating hospitals. We included all pregnant or peripartum patients (from the 13th week of gestation until the 1st week postpartum) with PCR-confirmed COVID-19 admitted to the ICU in which the reason for the ICU admission was respiratory complications of severe COVID-19 pneumonitis. Obstetric patients with confirmed COVID-19 who were admitted to the ICU for non-COVID-19 indications (eg, postpartum haemorrhage, preeclampsia, or trauma) were excluded unless they also had respiratory complications of COVID-19 pneumonitis that independently warranted ICU admission. A local coordinator at each centre identified patients meeting the inclusion criteria and assisted with data access. Patients were studied until death or hospital discharge. Patients who were admitted to one ICU and who were later transferred to another ICU were analysed as a single ICU admission.

Procedures

Upon ICU admission, we collected maternal demographic data (age, height, weight, BMI, comorbidities, and Acute Physiology and Chronic Health Evaluation II [APACHE-II] score[33]) and obstetric demographic data (gravidity, parity, gestational age, previous deliveries, and previous obstetric diagnoses). Dates of first positive SARS-CoV-2 PCR test, first onset of COVID-19 symptoms, and hospital and ICU admission were recorded.

We classified patients into groups: no-delivery (pregnant at admission and no delivery during the ICU stay), postpartum (ICU admission ≥1 day after delivery), delivery-critical (pregnant at admission and receiving or at high risk of requiring IPPV at the time of delivery), or delivery-non-critical (pregnant at admission and not critically ill at the time of delivery). The a priori criteria for classification of critical versus non-critical were determined by the expert panel (appendix p 1) before data analysis. To be categorised as critical, patients had at least one of the following criteria on the day of delivery: ECMO, invasive positive pressure ventilation (IPPV) for respiratory indications (not including for general anaesthesia unless IPPV was continued post-operatively for respiratory indications), partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2 [P/F]) ratio of less than 200, oxygen saturation/FiO_2 (SpO_2/FiO_2 [S/F]) ratio of less than 215, ratio of oxygenation (S/F ratio divided by respiratory rate [ROX index]) less than 4·5; all other patients were categorised as not critical on the day of delivery.

All data were collected by two researchers (EF and NLB) on site in each participating hospital, with the assistance of a local study representative. The demographic, clinical, and laboratory data, and x-rays were

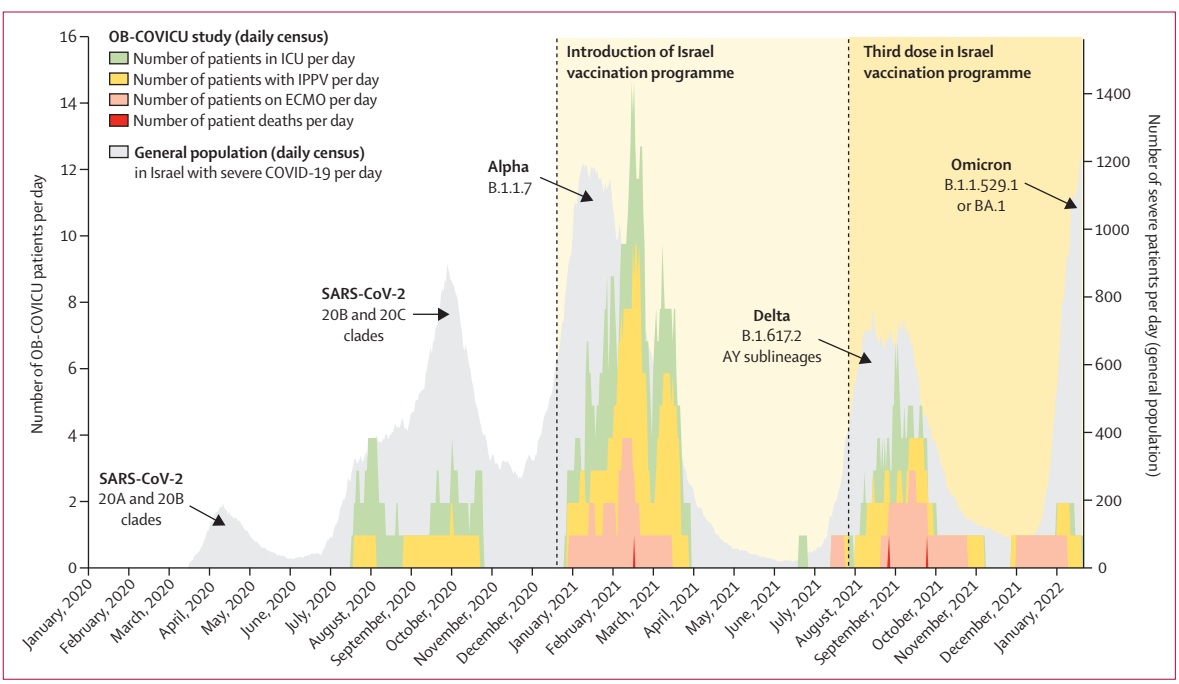

Figure 1: **Changes over time in the daily census of number of ICU admissions, use of mechanical ventilation, use of ECMO, and death among pregnant and postpartum patients during the study period Feb 1, 2020, to Jan 31, 2022**

ICU admission data for pregnant patients occurred predominantly in waves, corresponding to the national pandemic waves for the general population (marked with predominant viral strains). National census data were obtained from the Israel Ministry of Health COVID-19 dataset. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. IPPV=invasive positive pressure ventilation.

obtained from the electronic medical records and electronic or paper ICU charts. National census data were obtained from the Israel Ministry of Health.

All quantitative variables and data handling are presented in the appendix (pp 11–13).

Outcomes

The primary overall outcome measure was maternal outcome, determined as the worst of the following: no IPPV; IPPV use; ECMO use; or death. Thus, if more than one outcome occurred, the most severe outcome was used (ie, death > ECMO > IPPV > no IPPV). Patients receiving other respiratory support, including face mask, nasal cannula, high flow nasal cannula, continuous positive airway pressure, or bi-level positive airway pressure, but who never received IPPV, were classified as no IPPV.

The primary longitudinal outcome measure was the Sequential Organ Failure Assessment (SOFA) score,[34] measured at admission and on every morning of the ICU stay. Because the SOFA score was developed for sepsis with the potential for six-organ dysfunction or failure,[34] and because COVID-19 involves primarily pulmonary dysfunction and occasionally haemodynamic dysfunction,[35] we developed a novel score (the PORCH score) to be used in parallel with SOFA. The PORCH score is based on five key components that assess the severity of respiratory and cardiovascular derangement in COVID-19 (appendix pp 9–10): PEEP, oxygenation (same as for the modified SOFA score),[36] respiratory support, chest x-ray (using the 0–4 COVID-19 chest x-ray reporting and data system score [COX-RADS] chest x-ray severity score),[37] and haemodynamic support (similar to SOFA but using haemodynamic targets and vasopressor management protocols from the current Surviving Sepsis Campaign[38]). The daily PORCH score was the secondary longitudinal outcome measure. Other outcomes are included in the appendix (pp 11–13).

SOFA and PORCH scores were calculated by a study investigator (RC) who was blinded to the patient group and clinical outcomes. Excel formulae were very long (up to 900 characters per cell; appendix pp 14–16) and were checked manually and then password-protected to prevent transcription errors. The Excel formula sequence (=IF(cell="","",IF. . .) was used to prevent empty cells (eg, laboratory tests not performed every day) being recorded as zero. Duplicate quality assurance on all data was performed by two of the authors (EG and RC) and two other members of the OB-COVICU study group from Hadassah (N Galarza and S Burrows) to assess for data entry errors, transcription errors, formula errors, and cell formatting errors. We performed a random hand check of 5% of our patient sample against the original data entry sheets. We did not impute missing data because missing data accounted for less than 5% of our data, and there was no indication that missing data were distributed disproportionately in different patient groups.[39]

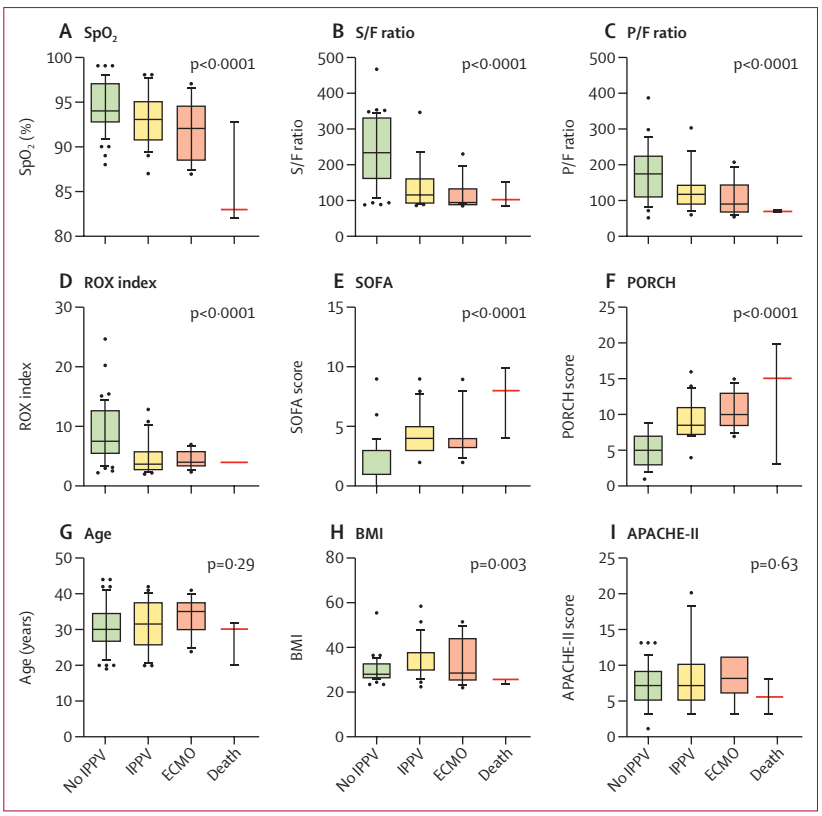

Figure 2: **Predictors of adverse maternal outcome**
For statistical analysis, adverse maternal outcome was assessed as a composite of IPPV–ECMO–death. (A–F) All measures of oxygenation at admission (SpO_2, S/F ratio, P/F ratio, and ROX index) and the SOFA and PORCH scores were highly predictive for the IPPV–ECMO–death composite (p<0·0001). (G–I) Unlike other published studies of COVID-19, age and comorbidities (APACHE-II) were not predictive for the IPPV–ECMO–death composite, which likely reflects the fact that all patients in the OB-COVICU study were pregnant females of childbearing age with few comorbidities. APACHE-II=Acute Physiology and Chronic Health Evaluation II. ECMO=extracorporeal membrane oxygenation. IPPV=invasive positive pressure ventilation. P/F ratio=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen. PORCH=PEEP, oxygenation, respiratory support, chest x-ray, haemodynamic support. ROX index=ratio of oxygenation (S/F ratio) to respiratory rate. SOFA=Sequential Organ Failure Assessment. S/F ratio=ratio of SpO_2 to fraction of inspired oxygen. SpO_2=oxygen saturation by pulse oximetry.

Statistical analysis

Data were inspected visually for normal distribution. Quantitative data are presented as median (IQR). We compared maternal quantitative outcomes using the Mann-Whitney test (two groups) or the Kruskal–Wallis test (>2 groups), or Fisher's exact test for categorical variables. We assessed whether there was evidence that the day of delivery was associated with either improvement or deterioration in repeated maternal measurements over time, between delivery-critical and delivery-non-critical groups, using mixed models repeated measures analysis, in which severity at time of delivery (non-critical *vs* critical) was defined as the between-groups effect, and day of delivery was a covariate. Assessment of time to ICU discharge (or death) used Kaplan-Meier survival models with log rank tests for comparing survival curves. A two-sided p value of less than 0·05 was considered statistically significant. When multiple comparisons were performed, Bonferroni

For more on the **Israel Ministry of Health COVID-19 dataset** see https://data.gov.il/dataset/COVID-19

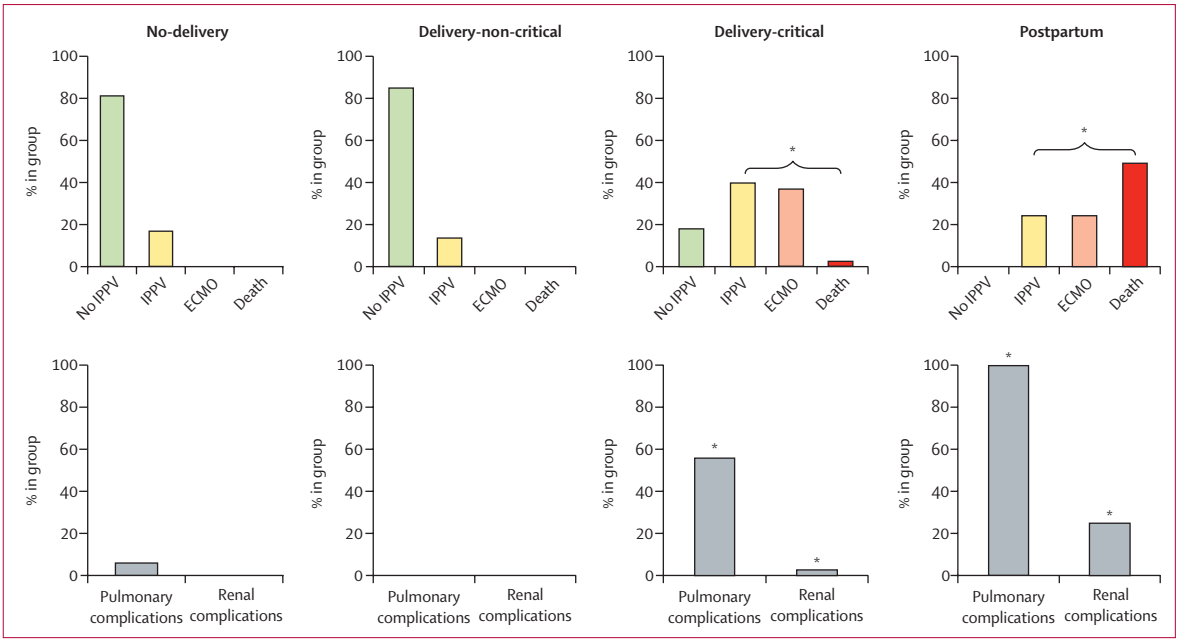

Figure 3: **Pooled data of maternal outcome by patient group**
Maternal outcome (worst of no IPPV, IPPV, ECMO, or death) is shown above the occurrence of pulmonary and renal complications for each group. The delivery-critical group and the postpartum group had markedly worse maternal outcomes. ECMO=extracorporeal membrane oxygenation. IPPV=invasive positive pressure ventilation. *Delivery-critical and postpartum groups versus other groups: p<0·0001.

correction was applied. Data were analysed using SPSS statistics program. Post-hoc power calculation for the Fisher's exact test of the primary endpoint was calculated using WinPepi (version 11.65). Graphs were prepared using GraphPad Prism (version 9.4.1) for Windows (GraphPad Software, San Diego, California USA) with pooled data presented as means (standard error).

For more on **WinPepi** see http://www.brixtonhealth.com/pepi4windows.html

Role of the funding source

There was no funding source for this study.

Results

Of 20 ICUs in Israel that accepted patients with COVID-19, five had no obstetric patients, one declined to participate, and one was inadvertently not approached. A total of 13 ICUs participated in the study. From Feb 1, 2020, to Jan 31, 2022, we identified 89 obstetric patients with COVID-19 who were admitted to 13 ICUs throughout Israel. Of these, five (6%) patients were excluded because they did not have symptomatic COVID-19 pneumonitis and were admitted to the ICU for other indications. 84 (94%) of 89 patients in 13 hospitals were analysed (appendix p 4). 46 (55%) of 84 patients delivered their baby during their ICU stay; 32 (70%) of 46 were classified as critical and 14 (30%) as non-critical on the day of delivery. There were four postpartum admissions, and 34 (41%) patients did not deliver during their ICU stay. Seven (8%) of 84 patients were transferred between ICUs. Two (2%) of 84 patients in the no-delivery group had no longitudinal clinical or arterial blood gas data (as hard paper charts had been lost) and were excluded from analyses of longitudinal data, but not from the outcome analysis. One critically ill patient in the delivery group had only partial data available as she was transferred from a non-participating hospital.

The frequency and severity of pregnant ICU patients with severe COVID-19 pneumonitis varied over the duration of the study. 64 (76%) of 84 patients were admitted during the 3rd wave, when alpha was the dominant variant (B.1.1.7), and the 4th wave, when delta was the dominant variant (B.1.617.2; figure 1).[40] All admissions that required ECMO (n=15) or who died (n=3) were admitted during these waves. There was marked diversity in disease severity at the time of ICU admission between different hospitals (appendix p 5).

In the pooled sample, variables incorporating measures of oxygenation (SpO_2, S/F ratio, P/F ratio, ROX index, SOFA score, PORCH score [p<0·0001]) and BMI (p=0·003) were significantly associated with adverse maternal outcome (figure 2). The following were not associated with adverse maternal outcome: age, APACHE-II, and the time until ICU admission from the onset of COVID-19 symptoms, from the diagnosis of COVID-19, or from the time of hospital admission (appendix p 8). The comorbidities of patients are presented in the appendix (p 17).

The delivery-critical and postpartum groups had worse maternal outcomes than all other groups (figure 3; appendix p 18). In the delivery-critical group, 26 (81%) of 32 patients received IPPV (the remainder received high flow nasal cannula), 12 (38%) received ECMO, and one (3%) died. In the small postpartum group, all

patients (four [100%] of four patients) received IPPV, three (75%) received ECMO, and two (50%) died. By contrast, only six (18%) of 34 patients in the no-delivery group and two (14%) of 14 patients in the delivery-non-critical group received IPPV; no patients in these groups received ECMO or died (figure 3). When assessing the IPPV–ECMO–death composite outcome, the incidence was two (14%) of 14 patients in the delivery-non-critical group versus 26 (81%) of 32 patients in the delivery-critical group (odds ratio [OR] 26 [95% CI 5–148]; p<0·0001; power 99%; figure 3).

Similarly, the delivery-critical and postpartum groups had a higher incidence of composite respiratory complications (pneumothorax, subcutaneous or mediastinal emphysema, ventilator-associated pneumonia; p<0·0001) and composite renal complications (acute kidney injury, acute renal failure, urinary tract infections, requirement for renal replacement therapy; p<0·0001; figure 3).

The SOFA and PORCH scores on ICU admission were worse for the delivery-critical and postpartum groups when compared with either the no-delivery or the delivery-non-critical groups (p<0·0001), and ICU stays were longer also in these groups (p<0·0001; figure 4). The median ICU stay in the delivery-critical group was 21 days (IQR 17–25), in the delivery-non-critical group was 4 days (2–7), in the postpartum group was 17 days (0–48), and in the no-delivery group was 7 days (6–8). The only significant difference between groups was between the delivery-critical or postpartum groups versus the no-delivery or delivery-non-critical groups (log rank Mantel-Cox p<0·0001). Other between-group comparisons were not significant. Patients who died (three [4%] of 84) represent censored data in the survival analysis.

To address the study's primary hypothesis, that the effect of delivery would be affected by the severity of the patient at the time of delivery, we assessed longitudinal SOFA and PORCH scores for the delivery group for the 5 days before delivery and the 10 days after delivery, in which data were stratified by critical and non-critical status on the day of delivery (figure 5). There was a marked difference between critical and non-critical groups in both SOFA (p<0·0001) and PORCH (p<0·0001) scores. Patients in the critical group had worse scores on ICU admission, deteriorated on the day of delivery, and took longer to recover, whereas those in the non-critical group improved rapidly after delivery. Accordingly, groups diverged following delivery; day of delivery was a highly significant covariate for the PORCH score (p<0·0001), but not for the SOFA score (p=0·09).

Longitudinal peripartum measures of oxygenation (SpO_2, S/F ratio, and P/F ratio), arterial blood gases (pH, partial pressure of arterial carbon dioxide, and base excess), and haemodynamic variables (heart rate and mean arterial pressure) are presented for both delivery-critical and delivery-non-critical groups (appendix p 8).

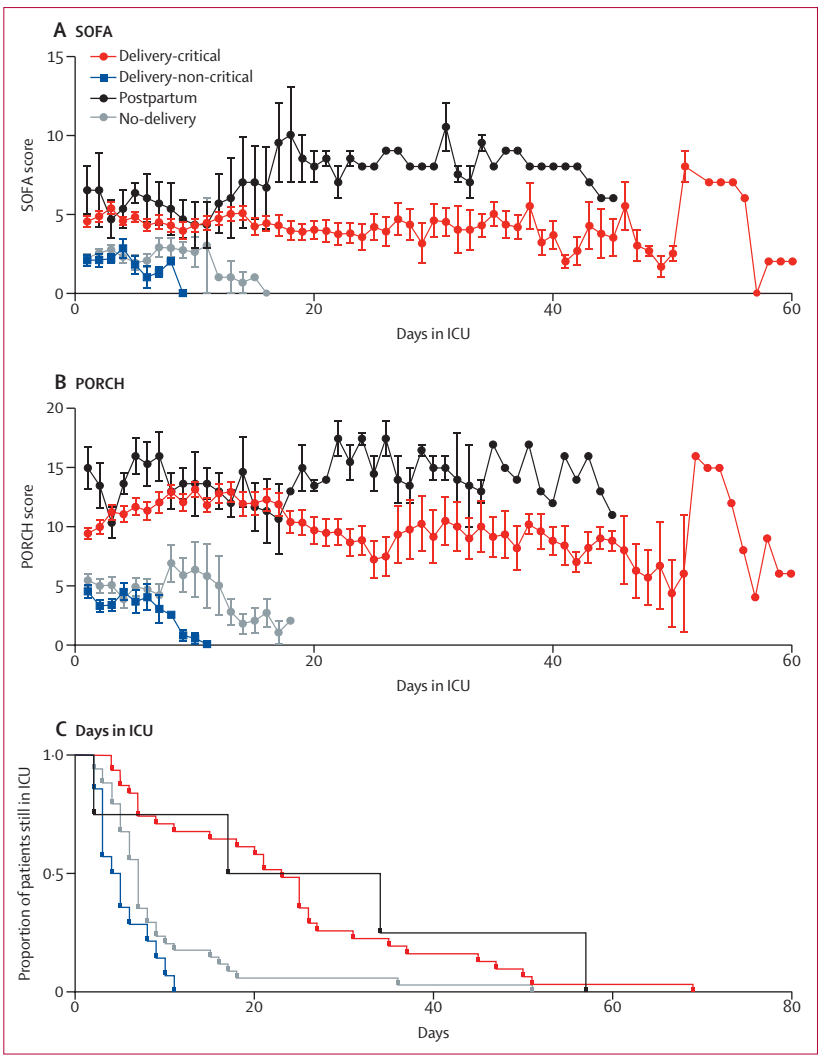

Figure 4: **Longitudinal severity scores and duration of ICU stay by patient group**
Pooled longitudinal SOFA scores (A), pooled longitudinal PORCH scores (B) for the entire ICU stay, and Kaplan-Meier cumulative survival analysis of ICU duration (C). There was a marked difference between groups (p<0·0001), with worse SOFA and PORCH scores on admission and slower trajectory of improvement, and longer ICU stay in both the delivery-critical and postpartum groups when compared with all other groups (p<0·0001). ICU=intensive care unit. PORCH=PEEP, oxygenation, respiratory support, chest x-ray, haemodynamic support. SOFA=Sequential Organ Failure Assessment.

Delivery was by caesarean section in all patients in the critical group, with 22 (69%) of 32 patients receiving general anaesthesia and 10 (31%) receiving regional anaesthesia. All patients receiving general anaesthesia were already intubated or required intubation for respiratory indications at the time of surgery. In the non-critical group, delivery was by caesarean section in 13 (93%) of 14 patients, with 2 (15%) of 13 caesarean sections performed under general anaesthesia, and 11 (85%) performed under regional anaesthesia; the one patient with induced vaginal delivery received epidural analgesia.

Median gestational age at delivery was preterm in both delivery groups (delivery-critical 32·0 weeks

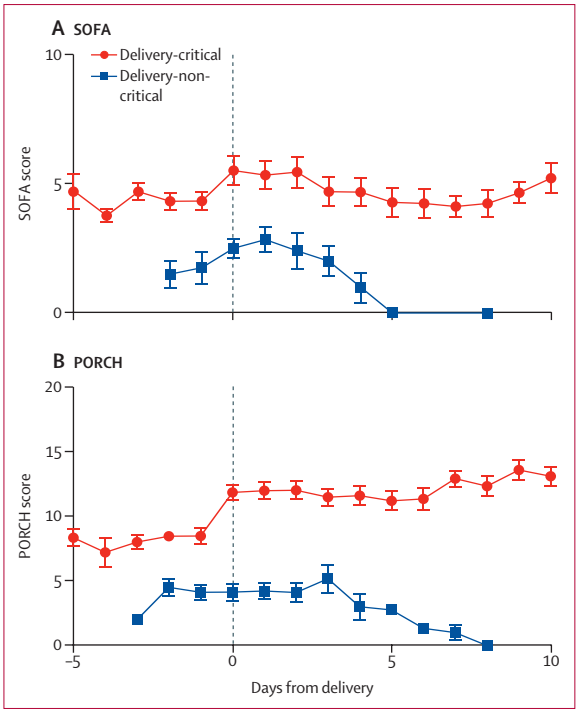

Figure 5: **Longitudinal SOFA (A) and PORCH (B) scores for the delivery-critical and delivery-non-critical groups**
Scores were recorded for 5 days before and 10 days after delivery. The day of delivery was a significant inflection-point covariate for the PORCH score (p<0·001) but not for the SOFA score (p=0·09). PORCH=PEEP, oxygenation, respiratory support, chest x-ray, haemodynamic support. SOFA=Sequential Organ Failure Assessment.

	Delivery-critical group (n=32)	Delivery-non-critical group (n=14)	p value
Demographic			
BMI	29·0 (9·3)	29·0 (7·5)	p=0·56
Gravida	4 (3)	3 (3)	p=0·17
Parity	2 (3)	2 (3)	p=0·37
Mode of delivery			
Caesarean delivery	32/32 (100%)	13/14 (93%)	Not analysed
Augmented labour with vaginal delivery	0	1/14 (7%)	Not analysed
Indication for interventional delivery			
Maternal respiratory deterioration	28/32 (88%)	7/14 (50%)	Not analysed
Fetal distress	0	4/14 (29%)	Not analysed
Both maternal respiratory deterioration and fetal distress	4/32 (13%)	2/14 (14%)	Not analysed
Outcome			
Gestational age at delivery, weeks	32·0 (4·0)	33·5 (4·3)	p=0·0040
Apgar score <7 at 1 min	13/28 (46%)	3/14 (21%)	Not analysed
Apgar score <7 at 5 min	8/28 (29%)	3/14 (21%)	p=0·72
Neonatal ICU	19/27 (70%)	7/14 (50%)	p=0·20
Neonatal intubation	9/27 (33%)	1/14 (7%)	p=0·13
Neonatal CPR	2/26 (8%)	2/14 (14%)	p=0·60
Neonatal death	1/30 (3%)	1/14 (7%)	p=0·54
Length of neonatal admission to hospital, days	17 (24)	15 (16)	p=0·10

Data are n/N (%), median (IQR), or mean (SD). ICU=intensive care unit. CPR=cardiopulmonary resuscitation.

Table: **Obstetric and neonatal demographics and outcomes**

[IQR 4·0] *vs* delivery-non-critical 33·5 weeks [4·3]; p=0·004; table); in the no-delivery group, the median gestational age at ICU admission was 28 weeks. The indication for delivery was predominantly maternal respiratory indications in both groups (table). There was a high incidence of neonatal ICU requirement and neonatal intubation. In the critical group, two (8%) of 26 neonates required cardiopulmonary resuscitation (CPR) and one (3%) of 30 neonates died; in the non-critical group there were two (14%) of 14 neonates who required CPR and one (7%) of 14 died. However, not one of the differences in neonatal outcomes was statistically significant (table).

Discussion

To our knowledge, this is the first report of longitudinal ICU data in the peripartum period from critically ill pregnant and postpartum patients with severe COVID-19 pneumonitis.

This national study shows that measures reflecting patient oxygenation at ICU admission were highly predictive for maternal outcome. Unlike previous reports from the non-pregnant[41] and pregnant population,[42] maternal age and APACHE-II score at admission were not associated with adverse outcomes. It is likely that this finding reflects the young age and lack of comorbidities in this cohort. The lack of comorbidities among Israeli pregnant patients with COVID-19 pneumonia has previously been reported.[43]

To our knowledge, this is also the first study to assess the effect of delivery in critically ill pregnant patients with severe COVID-19 pneumonia. In the two delivery groups, the response to delivery in terms of longitudinal clinical data was dependent on whether the patient was critical or non-critical at the time of delivery. It must be remembered, however, that these two groups were selected on the basis of severity. Nevertheless, it is clear from our data that the day of delivery was a point of divergence between the critical and non-critical groups. Among patients classified as non-critical on the day of delivery, no patients deteriorated following delivery. Indeed, there was a rapid, marked improvement in almost all clinical parameters during the first days after delivery, leading rapidly to ICU discharge. By contrast, patients in the critical group tended to deteriorate on the day of delivery and had a delayed recovery, with worse maternal outcome. Due to the observational study design and selection on the basis of severity for the two

groups that delivered in the ICU, we cannot conclude whether the critical patients deteriorated as a consequence of caesarean delivery, or whether surgery was performed urgently as a consequence of their sudden preoperative deterioration.

In addition to assessing critical and non-critical status on the day of delivery, we also assessed this status on the day of admission. There was not a single patient in our cohort who was classified as non-critical at admission and who deteriorated to become critical by the day of delivery. It is possible that many patients who were non-critical at admission would have remained not critical until they improved, even without delivery. Indeed, the trajectory for patient recovery in the non-critical delivery group was almost identical to that of the no-delivery group.

Among patients who underwent delivery during their ICU stay, maternal outcome was, as expected, far worse in patients defined as critical compared with non-critical. More surprising was the particularly poor maternal outcome among the small number of postpartum patients in our cohort. These patients were the most severe on admission, had the longest ICU stays, and had the worst maternal mortality. They also had the longest duration from hospital admission to ICU admission. We believe that these data warrant a reassessment of ICU admission criteria for postpartum patients with symptomatic COVID-19 pneumonitis, and that additional vigilance should be considered for postpartum patients managed in a non-ICU setting.

Almost all of the deliveries were by caesarean section and were performed preterm in our study. Concerns for maternal wellbeing typically take precedence over concerns for neonatal wellbeing in the presence of critical maternal illness,[44] and are the predominant factors driving clinical management. Although there were high rates of neonatal ICU admission and neonatal intubation in both groups of patients who delivered during their ICU stay, there were no significant differences in adverse neonatal outcomes between critical and non-critical patients. We cannot determine whether these adverse neonatal outcomes were related to the underlying maternal disease or the decision to perform interventional delivery.

There was a rapid increase in availability of ECMO teams and devices in Israeli hospitals in response to the pandemic, rising from 35 devices in 12 hospitals to 95 devices in 16 hospitals (Kassif Y, Israel ECMO Society, personal communication). In addition to the three (4%) of 84 patients who died, a further 13 (87%) of 15 patients receiving ECMO survived. Together these amount to 19% of all pregnant patients with COVID-19 in the ICU and 42% of all ventilated patients. We cannot speculate how many of these patients would have survived without ECMO. We can, however, assert that ECMO has become an important salvage strategy in pregnant women with critical COVID-19,[45,46] associated with high rates of survival.[46]

Study strengths include, first, the fact that this was a national study. Second, we enrolled a large number of consecutive pregnant patients admitted to the ICU with severe COVID-19 pneumonitis over a 24-month period that spanned successive waves of the pandemic, each with its own predominant viral strain and clinical presentation. Third, unlike other studies of pregnant patients with COVID-19 in the ICU,[24] this study collected not only maternal and neonatal outcome data, but also longitudinal daily data on ICU stay, which enabled temporal associations to be made between these longitudinal data and the timing of delivery. Finally, in parallel to the SOFA score, this study introduced the novel PORCH score. This score included three important aspects not addressed by the SOFA score that were probably more relevant in assessing severity in COVID-19 pneumonia, which primarily involves respiratory dysfunction. These three factors were the level of respiratory interventional support, the level of administered PEEP, and the radiological severity score of the pneumonitis.[47] Although the oxygenation component of PORCH is identical to that used in SOFA,[34] the recent haemodynamic component is more in line with haemodynamic targets and vasopressor management protocols.[38] The PORCH score will require a validation sample to evaluate its ability to assess patient severity and predict outcome.

The main limitation of the study was that it was not randomised and not controlled, and patient groups were selected on the basis of severity. Most data were collected retrospectively, although, for some patients, data were collected prospectively. Although our longitudinal data do allow us to make temporal associations between markers of maternal disease and the timing of delivery, between-group comparisons must be interpreted with caution, and we have been careful to avoid making any causal inferences. Second, our conclusion that interventional delivery should be considered for maternal indications before patients deteriorate and require IPPV assumes that some patients might be expected to deteriorate from a non-critical state (in our cohort, all non-critical patients improved rapidly following delivery) to a critical state (in our cohort, critical patients either deteriorated or did not improve) following delivery. Third, although this was a nationwide sample over 2 years, it is a small cohort of patients. Fourth, we only studied patients in the ICU; apart from the length of their hospital admission, we have no data on their pre-ICU or post-ICU care, vaccination status, long-term COVID-19 manifestations,[48] or long-term maternal or neonatal outcomes. Fifth, as the pandemic required COVID-19 ICUs to be created or expanded urgently, this pressure might have led to heterogeneous standards of care and record keeping. Finally, patients who died in the ICU represented censored data points for the duration of ICU stay.

Severe COVID-19 pneumonitis occurring during pregnancy is associated with major maternal morbidity

and mortality.[14,24,46] In this national study, we showed that 45% of patients were treated with IPPV, 15% of patients were treated with ECMO, and 4% of patients died.

We showed that patients receiving IPPV, or who were close to requiring IPPV, deteriorated on the day of delivery, took longer to recover, and had a worse maternal outcome. By contrast, all other patients in our study improved rapidly following delivery. Within the constraints of a predominantly retrospective study, and with no data from randomised controlled trials, our longitudinal data provide, to our knowledge, the best available evidence suggesting that when faced with a pregnant patient with severe COVID-19 pneumonitis who is not improving despite escalating oxygen therapy, early interventional delivery should be considered for maternal indications, and that delivery should not be delayed until patients are close to requiring IPPV. Furthermore, the small group of (<1 week) postpartum patients who exhibited higher morbidity and mortality were admitted to ICUs with more severe disease, and had a longer time between hospital admission and ICU admission than other groups. Therefore, we we advocate a reassessment of ICU admission criteria for postpartum patients with COVID-19 pneumonitis and the provision of additional vigilance if they continue to be managed in a non-ICU setting.

Contributors

YG conceived the study. EF and YG searched the literature. EF, PVvH, and YG designed the study. PVvH and YG provided research funding. EG, TB-A, NLB, EF, and RC collected the data. YG supervised the study. EF and YG administered the study. EG and EF curated the data. EG, RC, and two other members of the OB-COVICU study group (N Galarza and S Burrows) performed duplicate quality assurance on all data, assessed the data for entry errors, transcription errors, formula errors, and cell formatting errors. RC and TB-A performed the software analysis. EF, EG, TB-A, CLS, PVvH, and YG interpreted the data. EG, TB-A, and YG drew the figures. YG and EF wrote the original draft, AT, OG, SS, BMB, SE, RP, CLS, and PVvH edited the manuscript. All authors had access to the raw data and critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

Declaration of interests

The following received research time from Hadassah Hebrew University Medical Center, Jerusalem, Israel: EF (ICU fellowship project); NLB and RC (anesthesiology residency project); and YG (academic appointment). EG was paid as a research co-ordinator from educational funds of YG. TB-A was paid from educational funds of PVvH. All other authors declare no competing interests.

Data sharing

Pooled study data will be available from the corresponding author by request. Individual participant data will not be available.

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